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Cardiovascular toxicity of targeted therapies for cancer: a protocol for an overview of systematic reviews

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Abstract (max 300): 300

Body (max 4,000): 2,006 (Rationale, Objectives, Methods, Discussion)

Keywords: Overview, systematic review, cancer, targeted therapy, antineoplastic agent, cardiovascular toxicity

ABSTRACT

Introduction: The introduction of targeted therapies for cancer has contributed to dramatic improvements in patient survival. Nevertheless, several targeted therapies have been associated with 'off-target' adverse effects, such as cardiotoxicity, based on varying levels of evidence. To-date, this evidence has not been systematically synthesised. We will therefore synthesise published systematic review evidence of cardiovascular toxicity associated with targeted cancer therapies.

Methods and analysis: We will include systematic reviews of randomised controlled trials and observational studies that report on cardiovascular outcomes for individual agents. We will identify systematic reviews by applying a pre-developed, standardised search strategy executed across multiple databases. Two independent reviewers will identify reviews contingent upon pre-defined eligibility criteria. They will resolve ambiguous cases by reaching a consensus, arbitrated by a third reviewer if required. The reviewers will extract and report data according to methodological guidelines for overviews provided by the Cochrane Collaboration, Joanna Briggs Institute and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P). They will assess the quality of included reviews by applying the Assessment of Multiple Systematic Reviews (AMSTAR) tool. They will judge the quality of evidence in included reviews based on their assessment of bias and incorporation into the interpretation of findings. In synthesising the evidence, we will classify agents based on systematic review evidence of toxicity (sufficient, probable, possible, or indeterminate), for specific cardiovascular outcomes (congestive heart failure, myocardial infarction, ischemic heart disease, left ventricular ejection fraction decline, cerebrovascular disease, pulmonary embolism, thrombosis and hypertension). This will provide clinicians and patients with an accessible synthesis based on robust methodology.

Ethics and dissemination: Ethics approval is not required for overviews. We will conduct the study in collaboration with consumer representatives. We will submit results for peer-review publication, and disseminate them through established clinical and consumer networks.

Systematic review registration: PROSPERO number CRD42017080014.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- We will apply best-practice methodology in order to classify the cardiovascular toxicity of targeted therapies based on systematic-review evidence.
- Restriction to systematic reviews excludes newer agents for which systematic reviews have not yet been performed.
- Heterogeneity in systematic reviews, together with variable quality and completeness, prevents a quantitative synthesis of the evidence.
- Systematic review evidence has been almost exclusively generated from RCT populations that are younger and healthier than the average, newly diagnosed cancer patient.
- Short follow-up of the underlying RCTs may underestimate longer term cardiovascular toxicity.

RATIONALE

Cancer treatment has evolved considerably over the past two decades. The introduction of targeted therapies, including small molecule inhibitors, monoclonal antibodies, hormone therapies and immunotherapies, has contributed to dramatic improvements in patient survival. Paradoxically, evidence is accumulating that some of these agents are associated with a number of off-target adverse effects, including short- and longer-term cardiovascular toxicity. These include, but are not limited to left-ventricular ejection fraction (LVEF) decline, congestive heart failure (CHF), infarction, ischemia, arrhythmias, stroke, thromboembolism and hypertension.[1-3] The pathogenesis of cardiovascular toxicity associated with established chemotherapeutic agents, such as anthracyclines, has been well-described, whereas that for targeted therapies is less well understood. Moreover, there are no universally accepted evidence-based guidelines for monitoring or managing potential cardiovascular toxicity in patients exposed to these agents.[4 5]

Overviews of systematic reviews (also called *umbrella reviews*) compile information from multiple systematic reviews to provide a comprehensive synthesis of evidence.[6] Additionally, overviews of systematic reviews may provide a wider perspective on the heterogeneity, possible sources of bias and methodological quality of systematic reviews that may affect the credibility of evidence in a field.[7] There are no prior systematically conducted overviews of the cardiovascular toxicity of targeted cancer therapies. This overview will provide a comprehensive, accessible synthesis with which to inform clinicians in general practice and oncology when managing the cardiovascular health of cancer patients.

OBJECTIVES

We will synthesise published systematic review evidence of cardiovascular toxicity associated with targeted cancer therapies. For each agent for which there is systematic review evidence, cardiovascular toxicity will be classified as sufficient, probable, possible or indeterminate.

METHODS AND ANALYSIS

Protocol and registration

This protocol was designed in accordance with the methodological guidelines for overviews provided by the Cochrane Collaboration,[6] the Joanna Briggs Institute,[8] and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P; checklist provided).[9] It is registered on the International Prospective Register of Systematic Reviews (PROSPERO # CRD42017080014 ; http://www.crd.york.ac.uk/prospero).[10 11]

Eligibility criteria

Types of studies

We will include published, peer-reviewed systematic reviews and meta-analyses of Phase II-III randomised controlled trials (RCTs) and observational cohort studies of targeted therapies for cancer which provide meta-estimates for cardiovascular outcomes. We will not include systematic reviews published only in abstract form, nor network meta-analyses. We will include pooled analyses if the study was a systematic review, and collected individual-level data from all eligible studies.

Population

We will limit our overview to studies of human cancer patients and will exclude treatment for other indications. We will not restrict studies by cancer type, patient age or gender.

Interventions

Our definition of targeted therapies will include: small molecule inhibitors (protein kinase, proteasome and other small molecule inhibitors); monoclonal antibodies; hormone (endocrine) therapies; and immunotherapies included within the L01X, L02B and L04AX rubrics of the World Health Organisation (WHO) Anatomical Therapeutic Chemical (ATC) classification. This system classifies agents according to the primary therapeutic use of the main active ingredient. [12] We will not include sensitizers used in photodynamic/radiation therapy (photodynamic agents). We will include agents administered in both neoadjuvant and adjuvant settings. We will restrict, where possible, to studies of patients undergoing first-line therapy; we will exclude studies solely examining second-line therapy

Comparison

We will limit our overview to systematic reviews that compare the agent of interest to placebo, with or without concurrent chemotherapy, radiotherapy, surgery, or transplantation. We will exclude systematic reviews with one or more studies in which the agent of interest was directly compared to standard therapy, or in which the agent of interest was given in both the treatment and control arm.

Outcomes

We will include systematic reviews reporting meta-estimates for at least one cardiovascular outcome. We will consider all relevant diseases of the cardiovascular system, as defined according to the WHO International Classification of Diseases 10th Revision (ICD10)[13] (ICD-10 codes I10-I99), including, but not limited to: CHF, myocardial infarction, ischaemic heart

disease, LVEF decline, cerebrovascular disease, pulmonary embolism, thrombosis and hypertension. We will not include haematological toxicities such as thrombocytopenia.

Information sources and search strategy

We will conduct an exhaustive literature search across two biomedical citation databases, Embase and Medline, as well as the Cochrane Database of Systematic Reviews. Our proposed search strategy is based on predefined systematic review search filters provided by the BMJ Evidence Centre[14] and was developed with the aid of an experienced research librarian. Search terms comprise keywords related to cancer, drug therapy, adverse events, toxicity, systematic reviews, and meta-analyses. We will adapt the search strategy for each database (see Supplementary File 1). English language articles published up until December 2016 will be eligible. We will identify any additional reviews by searching reference lists.

Data collection

We will manage identified studies using EndNote X8.0.1 [Thomson Reuters 2016]. After initial duplicate removal, two reviewers (SL and CV) will independently screen titles and abstracts against eligibility criteria. They will retrieve studies that are potentially relevant in full-text format and will again check them against eligibility criteria to determine inclusion. They will resolve discrepancies in included studies through discussion and consultation with a third reviewer (MvL) if consensus cannot be reached. They will summarise search results using a PRISMA flow diagram.[15]

Two reviewers (SL, CV) will independently extract data from each included study using a predefined data extraction form, resolving discrepancies through discussion and consultation with a third reviewer (MvL) if consensus cannot be reached. They will pilot this form and refine accordingly. Where data reported within systematic reviews are inconsistent, they will

contact the authors directly for clarification; they will exclude systematic reviews with data irregularities that cannot be resolved by communication with the authors.

The reviewers will extract the following data items from each included study:

(1) Bibliographic details (author, publication year);

(2) Methodological characteristics (information sources, search end date, study design and aim, eligibility criteria, publication date range of included studies, agent and dose, intervention, defined cardiovascular outcome including grade [severity], length of follow-up, method of pooling and bias assessment, funding);

(3) Patient characteristics (age, sex, cancer or tumour type, prophylaxis);

(4) Results (number of studies included in meta-estimate, event rate in exposed and unexposed trial arms or patient populations, meta-estimate, risk of bias within included studies, risk of bias in meta-estimate);

Assessment of methodological quality of included reviews

Two reviewers (SL, CV) will independently appraise the methodological quality of included reviews using AMSTAR,[16 17] a validated and reliable tool.[18] They will resolve discrepancies in AMSTAR scores through discussion and consultation with a third reviewer (MvL) if consensus cannot be reached. They will not exclude studies based on their AMSTAR score; however, we will use AMSTAR scores when preparing our evidence synthesis to select the higher-quality study from completely overlapping systematic reviews, rather than double-counting events and participants from primary studies (see 'Data Synthesis').

Assessment of quality of evidence

There is no agreed method with which to evaluate the quality of evidence across systematic reviews.[19] The GRADE system, as applied in Cochrane reviews,[6] to assess the quality of evidence and strength of recommendations cannot be readily applied in overviews of systematic reviews.[19 20] Additionally, given the scope of this overview, it is not feasible to judge the quality of every primary study included in each systematic review. Nevertheless, the strict criteria on which we will base our synthesis will ensure that only those systematic reviews with detailed reporting on the quality of primary studies contribute to the evidence (see 'Data Synthesis').[19]

Data synthesis

We will consider the issue of overlapping primary studies prior to preparing our evidence synthesis. If there are multiple systematic reviews of the same agent in the same patient population, and for the same outcome, we will apply the following:

- if the primary studies are completely overlapping, then we will select the highest quality review;
- if the primary studies partially overlap, then we will retain both reviews if the lower-quality review consists of more than one-third new studies;
- if the primary studies do not overlap, then we will retain both reviews.

We will denote systematic reviews containing overlapping primary studies using appropriate footnotes; likewise, we will note systematic reviews removed from our evidence synthesis due to completely overlapping studies.

We will use forest plots to display published meta-estimates for each agent and cardiovascular outcome; however, we will not compute an overview meta-estimate due the

likelihood of considerable heterogeneity in study populations and cardiovascular outcomes between studies, the absence of essential meta-data (number of events, number of exposed and unexposed patients), and the lack of well-established quantification methods.[18]

We will present the findings as a narrative synthesis,[21] and will use a 'stop-light indicator'[8] for visualisation. For each cardiovascular outcome, we will classify individual agents into one of five categories based on the 'worst-case' scenario across published reviews by applying the criteria described in Table 1. We will classify agents as having sufficient (red), probable (orange), or possible (yellow) evidence of toxicity, sufficient evidence of no toxicity (white), or indeterminate (grey) evidence of toxicity. We will consider evidence to be sufficient if a systematic review is of high quality, assesses the quality of the primary studies, and identifies a statistically significant association based on at least 1,000 exposed patients.[22] [23] For each cardiovascular outcome, sufficient systematic review evidence of cardiovascular toxicity will supersede any other classification.

Table 1. Classification used to synthesise evidence from systematic reviews of targeted cancer therapies and cardiovascular toxicity

Classification for each cardiovascular event	Conditions
Sufficient systematic review evidence of toxicity	If the following were *all* met: (i) a statistically significant meta-estimate of effect ($p<0.05$); (ii) the review was either high quality (AMSTAR score ≥8) or moderate quality (AMSTAR score 4-7), provided that the AMSTAR elements 7 and 8 were met*; AND (iii) the number of patients exposed to the agent was ≥1000.
Probable systematic review evidence of toxicity	If the following are *all* met: (i) a statistically significant meta-estimate of effect ($p<0.05$); (ii) the review was either high quality (AMSTAR score ≥8) or moderate quality (AMSTAR score 4-7), provided that the AMSTAR elements 7 and 8 were met*; AND (iii) the number of patients exposed to the agent was <1000.
Probable systematic review evidence of toxicity	If the following are *all* met: (i) a statistically significant meta-estimate of effect ($p<0.05$); (ii) the review was moderate quality (AMSTAR score 4-7), without satisfying AMSTAR elements 7 or 8*, or of low quality (AMSTAR score ≤3); AND (iii) the number of patients exposed to the agent was ≥1000.
Possible systematic review evidence of toxicity	If the following are *all* met: (i) a statistically significant meta-estimate of effect ($p<0.05$); (ii) review was either moderate quality (AMSTAR score 4-7), without satisfying AMSTAR elements 7 or 8*, or low quality (AMSTAR score ≤3); AND (iii) the number of patients exposed to the agent was <1000.
Sufficient systematic review evidence of no toxicity	If the following are *all* met: (i) a statistically non-significant meta-estimate of effect ($p>0.05$); (ii) the review was either high quality (AMSTAR score ≥8) or moderate quality (AMSTAR score 4-7), provided that the AMSTAR elements 7 and 8 were met*; AND (iii) the number of patients exposed to the agent was ≥1000.
Indeterminate systematic review evidence of no toxicity	If the following are *all* met: (i) a statistically non-significant meta-estimate of effect ($p>0.05$); (ii) the review was either high quality (AMSTAR score ≥8) or moderate quality (AMSTAR score 4-7), provided that the AMSTAR elements 7 & 8 were met*; AND (iii) the number of patients exposed to the agent was <1000.
Indeterminate systematic review evidence of no toxicity	If the following are *all* met: (i) a statistically non-significant meta-estimate of effect ($p>0.05$); (ii) the review was moderate quality (AMSTAR score 4-7), without satisfying both AMSTAR elements 7 and 8*, or low quality (AMSTAR score ≤3); AND

	(iii) the number of patients exposed to the agent was of any size.
Indeterminate systematic review evidence of toxicity	If the only study examining the cardiovascular outcome did not report the number of patients exposed to the agent, regardless of effect or study quality.

* AMSTAR elements 7 and 8: quality of included studies was assessed, documented and used appropriately in formulating inclusions

ETHICS AND DISSEMINATION

Ethics approval is not required for overviews as they are based on published documents. We will conduct the study in collaboration with consumer representatives. We will submit our findings for peer-review publication and presentation at national and international conferences. We will also disseminate our findings through established clinical networks, as well as consumer networks, using lay summaries where appropriate.

DISCUSSION

This will be the first systematically conducted overview of cardiovascular toxicity associated with targeted cancer therapies. We will use robust methodology to rigorously appraise and comprehensively synthesise published systematic review evidence. Hierarchically, systematic reviews generally provide the highest level of evidence for harms associated with treatment.[24] However, overviews of systematic reviews present several methodological challenges that should be considered.[18 19 25] Firstly, using data more than once from individual primary studies without accounting for overlap may result in some primary studies being overrepresented. As recommended, we will apply *a priori* criteria to select systematic reviews when there are multiple potential candidates.[21]

Secondly, it is not feasible within this study to extract and assess risk of bias at the level of each individual primary study. Rather, our evidence synthesis will incorporate the quality of systematic reviews, the number of patients exposed, whether the quality of the primary studies was assessed, and the consistency of the evidence. These strict criteria will ensure that

low-quality systematic reviews that fail to assess or take into account the quality of the primary studies provide no more than indeterminate evidence in our synthesis.[19 26]

Thirdly, due to heterogeneity between systematic reviews in terms of outcomes and definitions, population characteristics, and study type and quality, a quantitative synthesis of the evidence is not possible.

Fourthly, restriction to published systematic reviews precludes inclusion of emerging evidence, and there is no agreed method for including additional primary studies.[27] Hence, we are unable to include in our synthesis evidence for those agents for which systematic reviews are yet to be conducted, and it will be inherently biased towards the more established agents.

Finally, despite our intention to include observational studies, evidence which is predominantly generated from RCTs may underestimate cardiovascular toxicity, as trial participants will be younger and healthier than the average cancer patient, and follow-up time may be insufficient to observe late effects. They are also unlikely to report detailed information on cardiovascular prophylaxis, such as use of angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers and beta-blockers, which are known to modify cardiovascular toxicity.1 4

Our evidence synthesis will provide new commentary on the current systematic review evidence for cardiovascular toxicity associated with individual targeted cancer therapies. It will provide an accessible, comprehensive synthesis with which to inform clinicians and the development of guidelines for the management of at-risk patients. Furthermore, it is expected that this overview will encourage further research for those agents for which systematic review evidence is currently insufficient or lacking.

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AUTHOR CONTRIBUTIONS

CV is the guarantor. MvL, SL, and CV drafted the protocol. All authors have made substantive intellectual contributions to the development of this protocol. MvL, SL, and CV developed the search strategy. HG, KW, and S-AP provided expertise on targeted therapies and MB on cardiovascular toxicity. LH contributed to the development of the stop-light indicator. All authors read, provided feedback and approved the final manuscript.

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COMPETING INTERESTS

The authors declare that they have no competing interests.

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Supplementary File 1 Proposed search strategies (EMBASE)

1	neoplasm$.mp. or exp neoplasms/
2	cancer.mp.
3	1 or 2
4	drug therapy.mp. or exp drug therapy/
5	biologic therapy.mp. or exp biologic therapy/
6	4 or 5
7	(ae or si or to or co).fs.
8	(safe or safety).ti,ab.
9	side effect$.ti,ab.
10	((adverse or undesirable or harm$ or serious or toxic) adj3 (effect$ or reaction$ or event$ or outcome$)).ti,ab.
11	exp adverse drug reaction/
12	exp drug toxicity/
13	exp intoxication/
14	exp drug safety/
15	exp drug monitoring/
16	exp drug hypersensitivity/
17	exp postmarketing surveillance/
18	exp drug surveillance program/
19	exp phase iv clinical trial/
20	(toxicity or complication$ or noxious or tolerability).ti,ab.
21	exp postoperative complication/
22	exp perioperative complication/
23	or/7-22
24	exp review/
25	(literature adj3 review$).ti,ab.
26	exp meta analysis/
27	exp "Systematic Review"/
28	or/24-27
29	(medline or medlars or embase or pubmed or cinahl or amed or psychlit or psyclit or psychinfo or psycinfo or scisearch or cochrane).ti,ab.
30	RETRACTED ARTICLE/
31	29 or 30
32	28 and 31
33	(systematic$ adj2 (review$ or overview)).ti,ab.
34	(meta?anal$ or meta anal$ or meta-anal$ or metaanal$ or metanal$).ti,ab.
35	32 or 33 or 34
36	3 and 6 and 23 and 35
37	36 not (conference abstract or conference paper or editorial).pt.
38	limit 37 to (human and english language and yr="1883-2016")

PRISMA-P (preferred reporting items for systematic review and meta-analysis protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No.	Checklist item	Yes	No
Administrative information				
Title:				
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☒
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	☒	☐
Authors:				
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☒
Support:				
Sources	5a	Indicate sources of financial or other support for the review	☒	☐
Sponsor	5b	Provide name for the review funder and/or sponsor	☐	☒
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☐	☒
Introduction				
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐
Methods				
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐

Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	☒	☐
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐
Study records:				
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	☒	☐
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	☐	☒
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	☐	☒
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	☐	☒
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	☒	☐
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	☒	☐

* Adapted from Table 2 in Shamseer et al (the PRISMA-P Group). Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ,* 2015;349:g7647.[9]

BMJ Open

Cardiovascular toxicity of targeted therapies for cancer: a protocol for an overview of systematic reviews

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Cardiovascular toxicity of targeted therapies for cancer: a protocol for an overview of systematic reviews

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Abstract (max 300): 300

Body (max 4,000): 2,101 (Rationale, Objectives, Methods, Discussion)

Keywords: Overview, systematic review, cancer, targeted therapy, antineoplastic agent, cardiovascular toxicity

ABSTRACT

Introduction: The introduction of targeted therapies for cancer has contributed to dramatic improvements in patient survival. Nevertheless, several targeted therapies have been associated with 'off-target' adverse effects, based on varying levels of evidence. To-date, this evidence has not been systematically synthesised. We will synthesise published systematic review evidence of cardiovascular toxicity associated with targeted cancer therapies.

Methods and analysis: We will include systematic reviews of randomised controlled trials and observational studies that report on cardiovascular outcomes for individual agents. We will identify systematic reviews by applying pre-developed, standardised search strategies within Embase, Medline and Cochrane Central. Two independent reviewers will identify reviews published up to 31 December 2016 using pre-defined eligibility criteria. They will resolve ambiguous cases through consensus, arbitrated by a third reviewer if required. The reviewers will extract and report data according to methodological guidelines for overviews provided by the Cochrane Collaboration, Joanna Briggs Institute and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P). They will assess the quality of included reviews by applying the Assessment of Multiple Systematic Reviews (AMSTAR) tool. They will judge the quality of evidence in included reviews based on their assessment of bias and incorporation into the interpretation of findings. In synthesising the evidence, we will classify agents based on systematic review evidence of toxicity (sufficient, probable, possible, or indeterminate), for specific cardiovascular outcomes (congestive heart failure, myocardial infarction, ischemic heart disease, left ventricular ejection fraction decline, cerebrovascular disease, pulmonary embolism, thrombosis and hypertension). This will provide clinicians and patients with an accessible synthesis based on robust methodology.

Ethics and dissemination: Ethics approval is not required for overviews. We will conduct the study in collaboration with consumer representatives. We will submit results for peer-review publication, and disseminate them through established clinical and consumer networks.

Systematic review registration: PROSPERO number CRD42017080014.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- We will apply best-practice methodology in order to classify the cardiovascular toxicity of targeted therapies based on systematic-review evidence.
- Restriction to systematic reviews excludes newer agents for which systematic reviews have not yet been performed.
- Heterogeneity in systematic reviews, together with variable quality and completeness, prevents a quantitative synthesis of the evidence.
- Systematic review evidence has been almost exclusively generated from RCT populations that are younger and healthier than the average, newly diagnosed cancer patient.
- Short follow-up of the underlying RCTs may underestimate longer term cardiovascular toxicity.

RATIONALE

Cancer treatment has evolved considerably over the past two decades. The introduction of targeted therapies, including small molecule inhibitors, monoclonal antibodies, hormone therapies and immunotherapies, has contributed to dramatic improvements in patient survival. Paradoxically, evidence is accumulating that some of these agents are associated with a number of off-target adverse effects, including short- and longer-term cardiovascular toxicity. These include, but are not limited to left-ventricular ejection fraction (LVEF) decline, congestive heart failure (CHF), infarction, ischemia, arrhythmias, stroke, thromboembolism and hypertension.[1-3] The pathogenesis of cardiovascular toxicity associated with established chemotherapeutic agents, such as anthracyclines, has been well-described, whereas that for targeted therapies is less well understood. Moreover, there are no universally accepted evidence-based guidelines for monitoring or managing potential cardiovascular toxicity in patients exposed to these agents.[4 5]

Overviews of systematic reviews (also called *umbrella reviews*) compile information from multiple systematic reviews to provide a comprehensive synthesis of evidence.[6] Additionally, overviews of systematic reviews may provide a wider perspective on the heterogeneity, possible sources of bias and methodological quality of systematic reviews that may affect the credibility of evidence in a field.[7] There are no prior systematically conducted overviews of the cardiovascular toxicity of targeted cancer therapies. This overview will provide a comprehensive, accessible synthesis with which to inform clinicians in general practice and oncology when managing the cardiovascular health of cancer patients.

OBJECTIVES

We will synthesise published systematic review evidence of cardiovascular toxicity associated with targeted cancer therapies. For each agent for which there is systematic review evidence, cardiovascular toxicity will be classified as sufficient, probable, possible or indeterminate.

METHODS AND ANALYSIS

Protocol and registration

This protocol was designed in accordance with the methodological guidelines for overviews provided by the Cochrane Collaboration,[6] the Joanna Briggs Institute,[8] and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P; checklist provided).[9] It is registered on the International Prospective Register of Systematic Reviews (PROSPERO # CRD42017080014 ; http://www.crd.york.ac.uk/prospero).[10 11]

Eligibility criteria

Types of studies

We will include published, peer-reviewed systematic reviews and meta-analyses of Phase II-III randomised controlled trials (RCTs) and observational cohort studies of targeted therapies for cancer which provide meta-estimates for cardiovascular outcomes. We will not include systematic reviews published only in abstract form, nor network meta-analyses. We will include pooled analyses if the study was a systematic review, and collected individual-level data from all eligible studies.

Population

We will limit our overview to studies of human cancer patients and will exclude treatment for other indications. We will not restrict studies by cancer type, patient age or gender.

Interventions

Our definition of targeted therapies will include: small molecule inhibitors (protein kinase, proteasome and other small molecule inhibitors); monoclonal antibodies; hormone (endocrine) therapies; and immunotherapies included within the L01X, L02B and L04AX rubrics of the World Health Organisation (WHO) Anatomical Therapeutic Chemical (ATC) classification. This system classifies agents according to the primary therapeutic use of the main active ingredient. [12] We will not include sensitizers used in photodynamic/radiation therapy (photodynamic agents). We will include agents administered in both neoadjuvant and adjuvant settings. We will restrict, where possible, to studies of patients undergoing first-line therapy; we will exclude studies solely examining second-line therapy. Systematic reviews consisting solely of second-line therapy trials, in particular multiple, small trials, were judged to be at high risk of non-random distribution of prior treatments to the trial arms, and thus potentially biased results.

Comparison

We will limit our overview to systematic reviews that compare the agent of interest to placebo, with or without concurrent chemotherapy, radiotherapy, surgery, or transplantation. We will exclude systematic reviews with one or more studies in which the agent of interest was directly compared to standard therapy, or in which the agent of interest was given in both the treatment and control arm.

Outcomes

We will include systematic reviews reporting meta-estimates for at least one cardiovascular outcome. We will consider all relevant diseases of the cardiovascular system, as defined according to the WHO International Classification of Diseases 10th Revision (ICD10)[13] (ICD-10 codes I10-I99), including, but not limited to: CHF, myocardial infarction, ischaemic heart disease, LVEF decline, cerebrovascular disease, pulmonary embolism, thrombosis and hypertension. We will not include haematological toxicities such as thrombocytopenia.

Information sources and search strategy

We will conduct an exhaustive literature search across two biomedical citation databases, Embase and Medline, as well as the Cochrane Database of Systematic Reviews. Our proposed search strategy is based on predefined systematic review search filters provided by the BMJ Evidence Centre[14] and was developed with the aid of an experienced research librarian. Search terms comprise keywords related to cancer, drug therapy, adverse events, toxicity, systematic reviews, and meta-analyses. We will adapt the search strategy for each database (see Supplementary File 1). English language articles published up until 31 December 2016 will be eligible. We will identify any additional reviews by searching reference lists. The search strategies were first applied on 1 May 2017 and the study is expected to conclude on 30 June 2018.

Data collection

We will manage identified studies using EndNote X8.0.1 [Thomson Reuters 2016]. After initial duplicate removal, two reviewers (SL and CV) will independently screen titles and abstracts against eligibility criteria. They will retrieve studies that are potentially relevant in full-text format and will again check them against eligibility criteria to determine inclusion. They will resolve discrepancies in included studies through discussion and consultation with

a third reviewer (MvL) if consensus cannot be reached. They will summarise search results using a PRISMA flow diagram.[15]

Two reviewers (SL, CV) will independently extract data from each included study using a predefined data extraction form, resolving discrepancies through discussion and consultation with a third reviewer (MvL) if consensus cannot be reached. They will pilot this form and refine accordingly. Where data reported within systematic reviews are inconsistent, they will contact the authors directly for clarification; they will exclude systematic reviews with data irregularities that cannot be resolved by communication with the authors.

The reviewers will extract the following data items from each included study:

(1) Bibliographic details (author, publication year);

(2) Methodological characteristics (information sources, search end date, study design and aim, eligibility criteria, publication date range of included studies, agent and dose, intervention, defined cardiovascular outcome including grade [severity], length of follow-up, method of pooling and bias assessment, funding);

(3) Patient characteristics (age, sex, cancer or tumour type, prophylaxis);

(4) Results (number of studies included in meta-estimate, event rate in exposed and unexposed trial arms or patient populations, meta-estimate, risk of bias within included studies, risk of bias in meta-estimate);

Assessment of methodological quality of included reviews

Two reviewers (SL, CV) will independently appraise the methodological quality of included reviews using AMSTAR,[16 17] a validated and reliable tool.[18] They will resolve discrepancies in AMSTAR scores through discussion and consultation with a third reviewer (MvL) if

consensus cannot be reached. They will not exclude studies based on their AMSTAR score; however, we will use AMSTAR scores when preparing our evidence synthesis to select the higher-quality study from completely overlapping systematic reviews, rather than double-counting events and participants from primary studies (see 'Data Synthesis').

Assessment of quality of evidence

There is no agreed method with which to evaluate the quality of evidence across systematic reviews.[19] The GRADE system, as applied in Cochrane reviews,[6] to assess the quality of evidence and strength of recommendations cannot be readily applied in overviews of systematic reviews.[19 20] Additionally, given the scope of this overview, it is not feasible to judge the quality of every primary study included in each systematic review. Nevertheless, the strict criteria on which we will base our synthesis will ensure that only those systematic reviews with detailed reporting on the quality of primary studies contribute to the evidence (see 'Data Synthesis').[19]

Data synthesis

We will consider the issue of overlapping primary studies prior to preparing our evidence synthesis. If there are multiple systematic reviews of the same agent in the same patient population, and for the same outcome, we will apply the following:

- if the primary studies are completely overlapping, then we will select the highest quality review;
- if the primary studies partially overlap, then we will retain both reviews if the lower-quality review consists of more than one-third new studies;
- if the primary studies do not overlap, then we will retain both reviews.

In our overview data summary tables we will denote systematic reviews containing overlapping primary studies using appropriate footnotes; likewise, we will explicitly note systematic reviews removed from our evidence synthesis due to completely overlapping studies. We will discuss the potential impact of these exclusions when reporting the evidence synthesis.

We will use forest plots to display published meta-estimates for each agent and cardiovascular outcome; however, we will not compute an overview meta-estimate due the likelihood of considerable heterogeneity in study populations and cardiovascular outcomes between studies, the absence of essential meta-data (number of events, number of exposed and unexposed patients), and the lack of well-established quantification methods.[18]

We will present the findings as a narrative synthesis,[21] and will use a 'stop-light indicator'[8] for visualisation. For each cardiovascular outcome, we will classify individual agents into one of five categories based on the 'worst-case' scenario across published reviews by applying the criteria described in Table 1. We will classify agents as having sufficient (red), probable (orange), or possible (yellow) evidence of toxicity, sufficient evidence of no toxicity (white), or indeterminate (grey) evidence of toxicity. We will consider evidence to be sufficient if a systematic review is of high quality, assesses the quality of the primary studies, and identifies a statistically significant association based on at least 1,000 exposed patients.[22] [23] For each cardiovascular outcome, sufficient systematic review evidence of cardiovascular toxicity will supersede any other classification.

Table 1. Classification used to synthesise evidence from systematic reviews of targeted cancer therapies and cardiovascular toxicity

Classification for each cardiovascular event	Conditions
Sufficient systematic review evidence of toxicity	If the following were *all* met: (i) a statistically significant meta-estimate of effect ($p<0.05$); (ii) the review was either high quality (AMSTAR score ≥8) or moderate quality (AMSTAR score 4-7), provided that the AMSTAR elements 7 and 8 were met*; AND (iii) the number of patients exposed to the agent was ≥1000.
Probable systematic review evidence of toxicity	If the following are *all* met: (i) a statistically significant meta-estimate of effect ($p<0.05$); (ii) the review was either high quality (AMSTAR score ≥8) or moderate quality (AMSTAR score 4-7), provided that the AMSTAR elements 7 and 8 were met*; AND (iii) the number of patients exposed to the agent was <1000.
Probable systematic review evidence of toxicity	If the following are *all* met: (i) a statistically significant meta-estimate of effect ($p<0.05$); (ii) the review was moderate quality (AMSTAR score 4-7), without satisfying AMSTAR elements 7 or 8*, or of low quality (AMSTAR score ≤3); AND (iii) the number of patients exposed to the agent was ≥1000.
Possible systematic review evidence of toxicity	If the following are *all* met: (i) a statistically significant meta-estimate of effect ($p<0.05$); (ii) review was either moderate quality (AMSTAR score 4-7), without satisfying AMSTAR elements 7 or 8*, or low quality (AMSTAR score ≤3); AND (iii) the number of patients exposed to the agent was <1000.
Sufficient systematic review evidence of no toxicity	If the following are *all* met: (i) a statistically non-significant meta-estimate of effect ($p>0.05$); (ii) the review was either high quality (AMSTAR score ≥8) or moderate quality (AMSTAR score 4-7), provided that the AMSTAR elements 7 and 8 were met*; AND (iii) the number of patients exposed to the agent was ≥1000.
Indeterminate systematic review evidence of no toxicity	If the following are *all* met: (i) a statistically non-significant meta-estimate of effect ($p>0.05$); (ii) the review was either high quality (AMSTAR score ≥8) or moderate quality (AMSTAR score 4-7), provided that the AMSTAR elements 7 & 8 were met*; AND (iii) the number of patients exposed to the agent was <1000.
Indeterminate systematic review evidence of no toxicity	If the following are *all* met: (i) a statistically non-significant meta-estimate of effect ($p>0.05$); (ii) the review was moderate quality (AMSTAR score 4-7), without satisfying both AMSTAR elements 7 and 8*, or low quality (AMSTAR score ≤3); AND

	(iii) the number of patients exposed to the agent was of any size.
Indeterminate systematic review evidence of toxicity	If the only study examining the cardiovascular outcome did not report the number of patients exposed to the agent, regardless of effect or study quality.

* AMSTAR elements 7 and 8: quality of included studies was assessed, documented and used appropriately in formulating inclusions

Patient and public involvement

We will conduct the study in collaboration with consumer representatives, including co-author Lee Hunt, who bring essential perspectives and experience to the multi-disciplinary investigative team. We will submit our findings for peer-review publication and presentation at national and international conferences. We will also disseminate our findings through established clinical networks, as well as consumer networks, using lay summaries where appropriate. Ethics approval is not required for overviews as they are based on published documents.

DISCUSSION

This will be the first systematically conducted overview of cardiovascular toxicity associated with targeted cancer therapies. We will use robust methodology to rigorously appraise and comprehensively synthesise published systematic review evidence. Hierarchically, systematic reviews generally provide the highest level of evidence for harms associated with treatment.[24] However, overviews of systematic reviews present several methodological challenges that should be considered.[18 19 25] Firstly, using data more than once from individual primary studies without accounting for overlap may result in some primary studies being overrepresented. As recommended, we will apply *a priori* criteria to select systematic reviews when there are multiple potential candidates.[21]

Secondly, it is not feasible within this study to extract and assess risk of bias at the level of each individual primary study. Rather, our evidence synthesis will incorporate the quality of

systematic reviews, the number of patients exposed, whether the quality of the primary studies was assessed, and the consistency of the evidence. These strict criteria will ensure that low-quality systematic reviews that fail to assess or take into account the quality of the primary studies provide no more than indeterminate evidence in our synthesis.[19 26]

Thirdly, due to heterogeneity between systematic reviews in terms of outcomes and definitions, population characteristics, and study type and quality, a quantitative synthesis of the evidence is not possible.

Fourthly, restriction to published systematic reviews precludes inclusion of emerging evidence, and there is no agreed method for including additional primary studies.[27] Hence, we are unable to include in our synthesis evidence for those agents for which systematic reviews are yet to be conducted, and it will be inherently biased towards the more established agents.

Finally, despite our intention to include observational studies, evidence which is predominantly generated from RCTs may underestimate cardiovascular toxicity, as trial participants will be younger and healthier than the average cancer patient, and follow-up time may be insufficient to observe late effects. They are also unlikely to report detailed information on cardiovascular prophylaxis, such as use of angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers and beta-blockers, which are known to modify cardiovascular toxicity.[1 4]

Our evidence synthesis will provide new commentary on the current systematic review evidence for cardiovascular toxicity associated with individual targeted cancer therapies. It will provide an accessible, comprehensive synthesis with which to inform clinicians and the development of guidelines for the management of at-risk patients. Furthermore, it is expected that this overview will encourage further research for those agents for which systematic

review evidence is currently insufficient or lacking.

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AUTHOR CONTRIBUTIONS

CV is the guarantor. MvL, SL, and CV drafted the protocol. All authors have made substantive intellectual contributions to the development of this protocol. MvL, SL, and CV developed the search strategy. HG, KW, and S-AP provided expertise on targeted therapies and MB on cardiovascular toxicity. LH contributed to the development of the stop-light indicator. All authors read, provided feedback and approved the final manuscript.

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COMPETING INTERESTS

The authors declare that they have no competing interests.

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Supplementary File 1 Proposed search strategies (EMBASE)

1	neoplasm$.mp. or exp neoplasms/
2	cancer.mp.
3	1 or 2
4	drug therapy.mp. or exp drug therapy/
5	biologic therapy.mp. or exp biologic therapy/
6	4 or 5
7	(ae or si or to or co).fs.
8	(safe or safety).ti,ab.
9	side effect$.ti,ab.
10	((adverse or undesirable or harm$ or serious or toxic) adj3 (effect$ or reaction$ or event$ or outcome$)).ti,ab.
11	exp adverse drug reaction/
12	exp drug toxicity/
13	exp intoxication/
14	exp drug safety/
15	exp drug monitoring/
16	exp drug hypersensitivity/
17	exp postmarketing surveillance/
18	exp drug surveillance program/
19	exp phase iv clinical trial/
20	(toxicity or complication$ or noxious or tolerability).ti,ab.
21	exp postoperative complication/
22	exp perioperative complication/
23	or/7-22
24	exp review/
25	(literature adj3 review$).ti,ab.
26	exp meta analysis/
27	exp "Systematic Review"/
28	or/24-27
29	(medline or medlars or embase or pubmed or cinahl or amed or psychlit or psyclit or psychinfo or psycinfo or scisearch or cochrane).ti,ab.
30	RETRACTED ARTICLE/
31	29 or 30
32	28 and 31
33	(systematic$ adj2 (review$ or overview)).ti,ab.
34	(meta?anal$ or meta anal$ or meta-anal$ or metaanal$ or metanal$).ti,ab.
35	32 or 33 or 34
36	3 and 6 and 23 and 35
37	36 not (conference abstract or conference paper or editorial).pt.
38	limit 37 to (human and english language and yr="1883-2016")

PRISMA-P (preferred reporting items for systematic review and meta-analysis protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No.	Checklist item	Yes	No	Page
Administrative information					
Title:					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☒	n/a
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	☒	☐	3
Authors:					
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	1 and online
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	14
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☒	n/a
Support:					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	14
Sponsor	5b	Provide name for the review funder and/or sponsor	☐	☒	n/a
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☐	☒	14
Introduction					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	4

Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	5-7
Methods					
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	5-7
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	☒	☐	7
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	7 and supplement
Study records:					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	7
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	☒	☐	7-8
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	7-8
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	8
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	6-7
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	8-10
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	☐	☒	n/a

	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	☐	☒	n/a
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	☐	☒	n/a
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	9-10
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	☒	☐	8
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	☒	☐	10

* Adapted from Table 2 in Shamseer et al (the PRISMA-P Group). Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ,* 2015;349:g7647.[9]